REMARKS

Claims 1, 6-9 and 18-20 are currently pending.

The invention

As a preliminary matter, the Examiner appears to misunderstand the disclosure in Applicants' specification, as well as the nature of Applicants' claimed invention.

Applicants' invention is premised on the following syllogism:

1. Immune response and immunopathology are mediated by cytokines;
2. Cytokines mediate immune response and immunopathology by *inter alia* effecting changes in gene expression of particular polynucleotides;
3. A composition comprising polynucleotides whose expression is modulated by cytokines are useful in a variety of applicaitons, for example, in obtaining expression profiles.

Applicants' specification is replete with supporting disclosure. The method for identifying the plurality of polynucleotides whose expression is modulated by cytokines and which together comprise the claimed composition is described, in general terms, at page 8, lines 5-16, and in detail in Examples VI through X, commencing at page 25, line 33.

Further, the Examiner has misconstrued the significance of the data appearing in Tables 1-4. Tables 1-4 are ***not*** tabulations of data obtained using the claimed compositions with the claimed methods, as the Examiner implies at page 5 of the Office Action. As Applicants indicate in the "Description of the Tables" at page 4 of the specification, Tables 1-4 instead show data regarding the degree to which the polynucleotide sequences of the claimed composition were differentially expressed in PBMC's from healthy individuals in response to cytokine treatment. This data provided the basis for selection of the polynucleotides included in the composition of claim 1.

Hence, the statement at page 5 of the Office Action, that "[t]he simple listing of speculated associated disorders as seen on page 29 does not directly correlate to the experimental data of altered gene expression observed in SEQ ID NO:1-516," demonstrates that the Examiner misunderstands the disclosure in the specification. With respect to the cytokine treatment protocol detailed in the aforementioned examples, nowhere in the application is there any indication that the cytokine treatments were intended to model any particular immune response or pathology, although they may have done so.

Applicants emphasize that the selection of polynucleotides for inclusion into the composition claimed by Applicants is distinct from the uses to which the claimed composition are then put, e.g.,generating expression profiles via, for example, the method of claim 7; screening samples from patients as in, for example, claims 18-20; detect the presence of a polynucleotide in a sample, as in, for example, the method of claim 7, or screening a library of molecules or compounds to identify a ligand, as in , for example, claims 8-9.

Rejection of claims 7-9 under 35 U.S.C. § 101

Claims 7-9 have been rejected under § 101 as allegedly lacking patentable utility. The Examiner reasons:

> "The specification disclosure implies that [the ligands and polynucleotides identified by the methods recited in claims 7-9] would provide information useful in diagnosis or treatment of disease. However, the fact that a hybridizing polynucleotide is present in a sample or a molecule that binds to the composition of claim 1 is identified does not provide in and of itself any information useful to diagnosis or treatment. The composition of claims 1 *[sic]* is insufficiently characterized for diagnosis and treatment (see enablement rejection below). As such these methods would provide no useful information and therefore lack a specific, substantial and credible utility."

See the Office Action at page 2-3.

Applicants respectfully disagree with the Examiner's reasoning, and traverse the rejection for at least the following reasons.

To begin with, the Examiner assumes that the claimed methods cannot provide any useful information absent complete functional characterization of the proteins encoded by the polynucleotides which together comprise the combination recited in claim 1. This is incorrect. As detailed in the specification (see page 17, line 32 to page 18, lne 6), the method of claim 7 can be used to generate standard expression profiles which may then be used as a basis for disease diagnosis and treatment monitoring. Given that expression of the polynucleotides which together comprise the claimed composition is known to be cytokine-modulated, the function of the proteins encoded by those polynucleotides is irrelevant. ***It is the profile of expression, i.e., the overall picture of changes in expression levels of all of the polynucleotides, that provides useful information***, for example, the existence or remission of a diseased state. See the specification at page 8, lines 13-16: "Since

polynucletoides are identified solely based on expression levels, it is not essential to know *a priori* the function of the particular gene. ***The overall pattern of expression is especially useful in characterizing expression patterns associated with an immune response due to an infection or an autoimmune disorder."*** [Emphasis added.].

The specific and substantial utility arises out of the pattern of expression of all the polynucleotides collectively, in that the pattern gives information, not just as to which polynucleotides exhibit changed expression, but as to the physiologic or pathologic condition of the subject from which the sample is taken.

Similarly, with respect to the methods of claims 8-9, it is the fact that the method identifies ligands which bind to polynucleotides whose expression is modulated by cytokines that is important and that provides the utility of the method. It is again irrelevant as to what proteins are encoded by the polynucleotides to which the ligands bind. Utility arises out of identifying ligands which, for example, may play a role in cytokine-modulated regulation of gene expression, and, once those ligands are identified, in purifying them. See Pge 13, lines 9-19.

Therefore, Applicants respectfully request that the rejection as to claims 7-9 be withdrawn.

Rejection of claims 1,6-9 and 18-20 under the written description requirement of 35 U.S.C. § 112, 1st paragraph

The Examiner has rejected claims 1, 6-9, and 18-20 as lacking sufficient written description. She asserts:

> "The sequences disclosed by the applicant lack written description due to the number of sequences within SEQ ID NOs:1-516 having unknowns or "unsure"s within the nucleic acid sequences. These wild cards do not disclose exactly that which was utilized by the applicant in order to accomplish the practice of the instant invention. The uncertainties create unknown sequences, each varying from the other by "a, t, c, g, or other" in many times more than just one location." See page 3 of the Office Action.

Applicants disagree, and traverse the rejection in this regard for at least the following reasons.

> "The Sequence Listing is a compilation of polynucleotides obtained by sequencing clone inserts (isolates) of different cDNAs and identified by hybrid complex formation using the cDNAs as probes on a microarray. Each sequence is identified by a sequence identification number (SEQ ID NO:) and by the Incyte clone ID from which it was obtained."

Applicants submit that the sequences in the Sequence Listing conform to CFR37 § 1.822 in which N is defined by reference to the tables in WIPO Standard St.25 (1998) Appendix 2, Tables 1 and 3.

Applicants also submit that Tables 1-4 as well as the Sequence Listing list the ***physical clone, i.e., the actual biological material,*** on which the sequences are based. For example, expression data for SEQ ID NO:1, corresponding to Incyte clone ID No. 068454H1, is listed in Table 1, and that clone and its library are listed in the Sequence Listing on page 1 at line <223>. Applicants reiterate that these clones identify actual biological material, cDNAs which were prepared as described in Example I of the specification, from mRNAs expressed in a cDNA library.

Thus, the fact that some of the sequences described in the sequence listing have undefined nucleotide residues does not mean that the identity of those residues is unknown, or unknowable, or that the entirety of the sequence was not in applicants' possession at the time of filing. It would be a simple matter to determine the identity of those residues by sequencing the clones in Applicants' possession using standard sequencing methods.

Applicants further submit that even if it were not described in EXAMPLE II, a person skilled in the art would know that the nucleotide sequences of the Sequence Listing had been prepared by automated methods. In early publications of sequences, it was commonly known and accepted that the sequence might contain occasional sequencing errors and unidentified nucleotides, but the physical clone was useful despite any unresolved base(s).

More recently, it has become standard practice for curators of databases to use N to mask those parts of sequences providing low information, such as repetitive elements, in order to optimize algorithmic searches for domains and motifs of far greater value. A recently issued Incyte patent, USPN 6,303,297, (filed 13 November 1997, on which Incyte Pharmaceuticals is the assignee) states in column 11, lines 53-57, "Low information sequences, although not necessarily informative in comparative analysis, are a part of the actual sequence, and thus are masked in the edited sequence instead of removed so that the low information sequence can be obtained in the database if necessary. These sequences are masked by substituting an N for the actual nucleotide (i.e. G, A, T, or C). This masks the low information sequences for search purposes but preserves the spacing of the DNA molecule. The actual sequences corresponding to the masked sequences are stored for informational

purposes." So Applicants further submit that the Ns in the claimed sequences do not hinder their use by one of skill in the art in various methodologies commonly using either the physical clone or sequence.

In early sequencing technology or this late in the genomics race, a person skilled in the art would know that these sequences represent biological material, could be obtained from commercial sources or using PCR and a cDNA library, and if desired, any particular N could be resolved using standard recombinant or database methodologies Recombinant technologies are provided in Sambrook et al. and Ausubel et al. as cited in the DESCRIPTION OF THE INVENTION on pages 13, lines 30-32 of the specification and at page 13, linle 33 to page 14, line 8 of the specificaiton, and enabled in Examples II-IV of the specification. Commonly available assembly software and the sequences in the NCBI public databases may also be used to assemble the sequences and resolve N as enabled in Examples II and IV.

Finally, Applicants submit that the Examiner has failed to provide any sequences or literature to show that any N in these sequences represents a site of variability (i.e., any particular N_x = A and T in different alleles).

With the remarks above, Applicants respectfully request that the rejection of claims 8, 11, 12, 16 and 21 under 35 USC § 112, first paragraph, be withdrawn and that the present application be allowed.

Regarding the rejection of claim 9 on the grounds that "mimetics" and "peptide nucleic acids" in lines 1-2 of claim 9 allegedly lack sufficient written description, Applicants disagree, and respectfully traverse the rejection. However, in the interest of expediting prosecution, these terms have been deleted from claim 9, thereby rendering the rejection moot in this respect. Applicants therefore respectfully request that it be withdrawn.

Rejection of claims 1, 6 and 18-20 under the enablement requirement of 35 U.S.C. § 112, 1st paragraph,

Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of lack of enablement, and therefore traverse the rejection for at least the following reasons.

MPEP 2164.04 provides:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." [Emphasis added.]

With respect to claims 1 and 6, Applicants have adequately described how to make the claimed composition by providing a sequence listing describing the polynucleotide sequences of the plurality of polynucleotides which together comprise that composition. They have adequately described how to use the composition by virtue of their descriptions of a number of methods of use which appear throughout the specification. An example of such a method is Example X, appearing at page 30, wherein they describe probe preparation, target labeling, and hybridization analysis.

Applicants have also adequately enabled the screening method recited in claims 18-20. In particular, Applicants describe how to use expression profiles to diagnose particular conditions at page 17, line 11 to page 18, line 6, and to evaluate the efficacy of a particular therapeutic treatment regiment or monitor the treatment of individual patients at page 18, lines 7-12.

The rejection appears to be based on the fact that Applicants have not provided examples wherein the claimed composition was used to generate expression profiles correlated with particular immune responses, immunopathologies, or "normal" states. However, Applicants respectfully submit that the absence of such examples is not tantamount to lack of enablement. In the first place, generating such expression profiles using the claimed combination with, for example, the method of claim 7, is well within the scope of Applicant's disclosure. See the disclosure at page 17, line 32 to page 18, line 6, and Example X at page 30. Further, generating such profiles would not require undue experimentation. Even assuming for purposes of argument that substantial numbers of samples would have to be screened in order to generate "standard" profiles, the quantity of experimentation is but one factor to be considered in determining whether the experimentation required to practice the invention is undue. ""The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it

is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt,* 190 USPQ 214, 217-19 (CCPA 1976)). Applicants submit that, in the present case, generating standard profiles, while certainly time consuming and possibly expensive, would be routine given the amount of guidance in the specification and given that Applicants have already identified the polynucleotides which would be most likely to exhibit changes.

Therefore, Applicants respectfully request that the enablement rejection be withdrawn.

Rejection of claims 8, 9 and 20 for indefiniteness under 35 U.S.C. § 112, second paragraph

The Examiner allege that claims 8 and 9 are indefinite due to the use of the word "specific," on the grounds that the term is relative and that the specification allegedly does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would therefore not be reasonably apprised of the scope of the invention. Applicants respectfully disagree, and traverse the rejection for at least the following reasons.

Applicants agree with the Examiner that "specific" is a relative term. In common usage, the term "specific binding" denotes binding that exceeds background levels. Applicants' specification describes an assay which employs the claimed method at page 13, lines 9-15. That description does not specify either the conditions or the degree of binding exhibited by the ligand identified. Applicants submit that, given the description in the specification, the common meaning of the term, and the plain language of the claim, the claim would be construed as contemplating that the conditions which allow specific binding may be varied in order that a skilled person could identify ligands capable of varying degrees of binding specificity. Given that Applicants claim a method of screening, which method may be employed using a variety of conditions, and that the term "specific" in common usage denotes binding that exceeds background, Applicants respectfully submit that the claim is sufficiently definite to appraise the public of the scope of their invention.

Use of phrase "immune response, disorder, condition or disease" in claim 18 is alleged to render that claim, as well as claims 19 and 20, indefinite. In light of the amendments to claim 18, wherein "disorder, condition or disease" are further specified to be "immune disorder, immune condition, or

immune disease," Applicants submit that the rejection has been rendered moot, and that the rejection should be withdrawn.

Use of "change" in claim 18 is alleged to render the claim indefinite. Claim 18 has been amended to indicate that the observed change that indicates the presence of the immune response, etc., occurs in the sample and is ascertained by comparison to the standard. Applicants submit that the rejection has thereby been rendered moot, and respectfully request that it be withdrawn.

Claim 20 has been amended to delete the phrase "other atopic disorders," thereby rendering the indefiniteness rejection moot; Applicants therefore respectfully request that it be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Please charge Deposit Account No. **09-0108** in the amount of **$920.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: 21 March 2002

Cathleen M. Rocco
Reg. No. 46,172
Direct Dial Telephone: (650) 845-4587

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 9, 18 and 20 have been amended as follows:

1. (As Once Amended) A composition comprising a plurality of polynucleotides whose expression is modulated by cytokines, wherein the polynucleotides are SEQ ID NOs:1-516 or a complete complement of SEQ ID NOs:1-516.

6. The composition of claim 1, wherein the polynucleotides are immobilized on a substrate.

7. (As Once Amended) A method for detecting a polynucleotide in a sample, the method comprising:

a) hybridizing the composition of claim 1 with the sample, thereby forming at least one hybridization complex; and

b) detecting the hybridization complex, wherein the presence of the hybridization complex indicates the presence of the polynucleotide in the sample.

8. (As Once Amended) A method of screening a library of molecules or compounds to identify a ligand, the method comprising:

a) combining the composition of claim 1 with a library of molecules or compounds under conditions to allow specific binding; and

b) detecting specific binding, thereby identifying a ligand.

9. (Once Amended) The method of claim 8 wherein the library is selected from DNA molecules, RNA molecules, [peptide nucleic acids, mimetics,] peptides, and proteins.

18. (Twice Amended) A method of screening a sample from a patient for an immune response, immune disorder, immune condition, or immune disease, the method comprising:

a) contacting the sample with the composition of claim 1 immobilized on a substrate under conditions to allow formation of a hybridization complex;

b) quantifying complex formation; and

c) comparing complex formation with a standard, wherein a change in the amount of complex formation in the sample relative to the standard indicates the presence of the immune response, immune disorder, immune condition, or immune disease.

19. The method of claim 18, wherein the immune disorder, condition, or disease is a pro-inflammatory disorder selected from viral infections, rheumatoid arthritis, insulin-dependent diabetes mellitus, multiple sclerosis, encephalomyelitis, inflammatory bowel disease, psoriasis, and pemphigus vulgaris.

20. (Twice Amended) The method of claim 18, wherein the immune disorder, condition, or disease is an anti-inflammatory disorder selected from bacterial and parasitic infections, allergies[and other atopic disorders], chronic graft versus host disease, scleroderma, and systemic lupus erythematosus.